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(71) Applicant *(for all designated States except US)*: **LIGAND PHARMACEUTICALS INCORPORATED** [US/US]; 10275 Science Center Drive, San Diego, CA 92121-1117 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ZHI, Lin** [CN/US]; 3988 Via Cangrejo, San Diego, CA 92130 (US). **VAN OEVEREN, Cornelis, Arjan** [NL/US]; 3635 Promontory Place, Carlsbad, CA 92008 (US).

(74) Agent: **PAGLIERY, Richar, H.**; Paul, Hastings, Janofsky & Walker LLP, P.O. Box 919092, San Diego, CA 92191-9092 (US).

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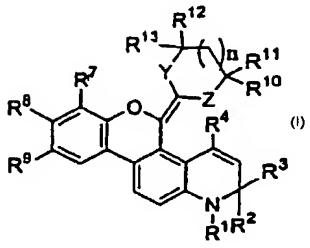
(54) Title: 5-(1',1'-CYCLOALKYL/ALKENYL)METHYLIDENE 1,2-DIHYDRO-*5H*-CHROMENO[3,4-*f*]QUINOLINES AS SELECTIVE PROGESTERONE RECEPTOR MODULATOR COMPOUNDS



(I)

(57) Abstract: The present invention is directed to compounds, pharmaceutical compositions, and methods for modulating processes mediated by Progesterone Receptor. Also provided are methods of making such compounds and pharmaceutical compositions. A compound of the formula (I), wherein R^1 is selected from the group of hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 heteroalkyl, COR^5, $C0_2R^5$, $S0_2R^5$, and $CONR^5R^6$; R^2 and R^3 each independently is selected from the group of hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; or R^2 and R^3 taken together form a cycloalkyl ring of from three to twelve carbons; R^7 through R^9 each independently is selected from the group of hydrogen, F, Cl, Br, I, NO_2, CN, OR^5, NR^5R^6, SR^5, COR^5, $C0_2R^5$, $CONR^5R^6$, C_1-C_8 alkyl, C_1-C_8 heteroalkyl, C_1-C_8 haloalkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl; Y and Z each independently is selected from the group of O, S, NR^6 and $CR^{14}R^{15}$; n is 0, 1, 2, or 3.

5-(1',1'-CYCLOALKYL/ALKENYL)METHYLIDENE 1,2-DIHYDRO-*5H*-CHROMENO[3,4-*f*]QUINOLINES AS SELECTIVE PROGESTERONE RECEPTOR MODULATOR COMPOUNDS

FIELD OF THE INVENTION

This invention relates to nonsteroidal 5-(1',1'-cycloalkyl/alkenyl)methylidene 1,2-dihydro-5H-chromeno[3,4-f]quinolines that may be modulators (*i.e.*, agonists, partial agonists and antagonists) of progesterone receptors and to methods for the making and use of such compounds.

BACKGROUND OF THE INVENTION

Progesterone receptor (PR) modulators have been widely used in regulation of female reproduction systems and in treatment of female hormone dependent diseases. The effectiveness of known steroidal PR modulators is often tempered by their undesired side-effect profile, particularly during long-term administration. For example, the effectiveness of synthetic progestins, such as norgestrel, as female birth control agents must be weighed against the increased risk of breast cancer and heart disease. Similarly, the progesterone antagonist, mifepristone (RU486), if administered for chronic indications, such as uterine fibroids, endometriosis and certain hormone-dependent cancers, could lead to homeostatic imbalances in a patient due to its inherent cross-reactivity as a glucocorticoid receptor (GR) antagonist. Accordingly, identification of compounds that have good receptor-selectivity for PR over other steroid hormone receptors as well as good tissue-selectivity (e.g., selectivity for uterine tissue over breast tissue) would be of significant value in the improvement of women's health.

A group of nonsteroidal molecules, which contain a di- or tetra-hydroquinoline ring as core pharmacophore (Todd, Jones; *et al.* US Patent Nos. 5,693,646; 5,693,647

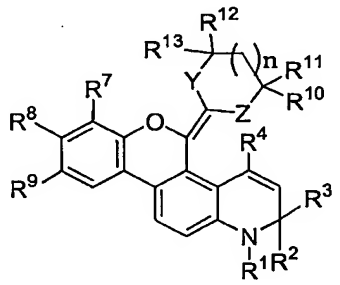
and 5,696,127) (M.J. Coghlan *et al.*, PCT Publication Nos. WO 99/41256 A1 and WO 99/41257 A1) have been described as steroid receptor modulator compounds.

The entire disclosures of the publications and references referred to herein are incorporated by reference herein and are not admitted to be prior art.

SUMMARY OF THE INVENTION

The present invention is directed to compounds, pharmaceutical compositions, and methods for modulating processes mediated by Progesterone Receptor. More particularly, the invention relates to nonsteroidal compounds and compositions which may be high affinity, high specificity agonists, partial agonists (*i.e.*, partial activators and/or tissue-specific activators) and/or antagonists for progesterone receptors. Also provided are methods of making such compounds and pharmaceutical compositions.

Compounds of the present invention may be represented by the formulae:



(I)

wherein:

R^1 is selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 haloalkyl, C_1–C_4 heteroalkyl, COR^5, CO_2R^5, SO_2R^5, and $CONR^5R^6$;

R^2 and R^3 each independently is selected from the group of hydrogen, C_1–C_6 alkyl, and C_1–C_6 haloalkyl; or

R^2 and R^3 taken together form a cycloalkyl ring of from three to twelve carbons;

R^4 is selected from the group of hydrogen, F, Cl, Br, CN, OR^5, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl;

R^5 and R^6 each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^7 through R^9 each independently is selected from the group of hydrogen, F, Cl, Br, I, NO_2, CN, OR^5, NR^5R^6, SR^5, COR^5, CO_2R^5, $CONR^5R^6$, C_1–C_8 alkyl, C_1–C_8 heteroalkyl, C_1–C_8 haloalkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl;

R^{10} through R^{15} each independently is selected from the group of hydrogen, F, Cl, Br, OR^5, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl; or

R^{12} and R^{14} taken together form a bond, when Y is $CR^{14}R^{15}$; or

R^{10} and R^{14} taken together form a bond, when Z is $CR^{14}R^{15}$;

Y and Z each independently is selected from the group of O, S, NR^6 and $CR^{14}R^{15}$;

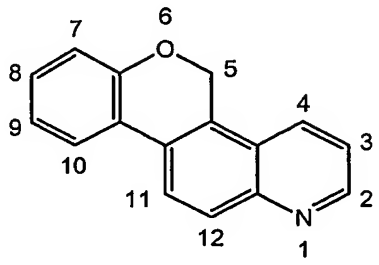
n is 0, 1, 2, or 3;

and pharmaceutically acceptable salts and prodrugs thereof.

DEFINITIONS AND NOMENCLATURE

As used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise. Furthermore, in an effort to maintain consistency in the naming of compounds of similar structure but differing substituents, the compounds described herein are named according to the following general guidelines. The numbering system for the location of substituents on such compounds is also provided.

A *5H*-chromeno[3,4-*f*]quinoline is defined by the following structure:



The term "alkyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain or cyclic-chain alkyl radical having from 1 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having from 1 to about 6 carbon atoms as well as those having from 1 to about 4 carbon atoms. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-amyl, pentyl, hexyl, heptyl, octyl and the like.

The term "alkenyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon double-bonds and having from 2 to about 18 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon double bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, 1,3-butadienyl and the like.

The term "alkynyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon triple-bonds and having from 2 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-

carbon triple bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, butynyl and the like.

The term "heteroalkyl" refers to alkyl groups, as described above, in which one or more skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof. The term heteroalkyl also includes alkyl groups in which one 1 to about 6 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof, as well as those in which 1 to 4 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof and those in which 1 to 2 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof.

The term "halogen" includes F, Cl, Br and I.

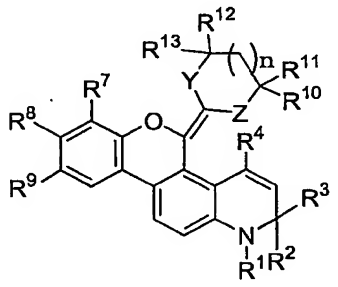
The term "mediate" means affect or influence. Thus, for example, conditions mediated by a progesterone receptor are those in which a progesterone receptor plays a role. Progesterone receptors are known to play a role in conditions including, for example, infertility, contraception, pregnancy maintenance and termination, female hormone deficiency, female sexual dysfunction, dysfunctional uterine bleeding, endometriosis, mood disorder, osteoporosis, and hormone-dependent cancers.

The term "selective" refers to compounds that display reactivity towards a particular receptor *(e.g.*, a progesterone receptor) without displaying substantial cross-reactivity towards another receptor (*e.g.*, glucocorticoid receptor). Thus, for example, selective compounds of the present invention may display reactivity towards progesterone receptors without displaying substantial cross-reactivity towards other steroid hormone receptors.

The term "modulate" means affect or influence. Thus, compounds that "modulate" a receptor affect the activity, either positively or negatively, of that receptor. The term may be used to refer to the activity of compounds of a receptor as, for example, an agonist, partial agonist or antagonist. The term also may be used to refer to the effect that a compound has on a physical and/or physiological condition of an individual. For example, certain compounds of the present invention may be used to modulate fertility in an individual. That is, certain compounds of this invention may be used to increase the fertility of an individual, while other compounds of this invention may be used to decrease the fertility of an individual.

DETAILED DESCRIPTION OF THE INVENTION

Compounds of the present invention may be represented by the formulae:



(I)

wherein:

R^1 is selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 haloalkyl, C_1–C_4 heteroalkyl, COR^5, CO_2R^5, SO_2R^5, and $CONR^5R^6$;

R^2 and R^3 each independently is selected from the group of hydrogen, C_1–C_6 alkyl, and C_1–C_6 haloalkyl; or

R^2 and R^3 taken together form a cycloalkyl ring of from three to twelve carbons;

R^4 is selected from the group of hydrogen, F, Cl, Br, CN, OR^5, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl;

R^5 and R^6 each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^7 through R^9 each independently is selected from the group of hydrogen, F, Cl, Br, I, NO_2, CN, OR^5, NR^5R^6, SR^5, COR^5, CO_2R^5, $CONR^5R^6$, C_1–C_8 alkyl, C_1–C_8 heteroalkyl, C_1–C_8 haloalkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl;

R^{10} through R^{15} each independently is selected from the group of hydrogen, F, Cl, Br, OR^5, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl; or

R^{12} and R^{14} taken together form a bond, when Y is $CR^{14}R^{15}$; or

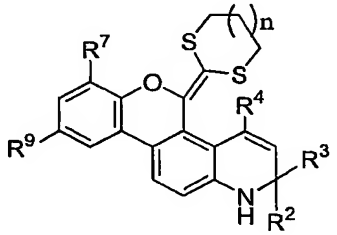
R^{10} and R^{14} taken together form a bond, when Z is $CR^{14}R^{15}$;

Y and Z each independently is selected from the group of O, S, NR^6 and $CR^{14}R^{15}$;

n is 0, 1, 2, or 3;

and pharmaceutically acceptable salts and prodrugs thereof.

Compounds of the invention include those represented by the formulae:



(II)

wherein:

R^2 and R^3 each independently is selected from the group of C_1–C_4 alkyl, and C_1–C_4 haloalkyl;

R^4 is selected from the group of hydrogen, F, Cl, Br, CN, OR^5, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl;

R^5 and R^6 each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^7 through R^9 each independently is selected from the group of hydrogen, F, Cl, Br, CN, OR^5, NR^5R^6, SR^5, COR^5, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, C_1–C_4 haloalkyl, C_2–C_4 alkenyl;

n is 0, 1, 2, or 3;

and pharmaceutically acceptable salts and prodrugs thereof.

In one aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a progesterone receptor modulator compound according to any one of formulae I and II shown above wherein R^1 through R^{15}, n, Y and Z all have the same definitions as given above.

In another aspect, the present invention comprises a method of modulating a process mediated by a progesterone receptor comprising administering to a patient having a condition mediated by a PR a pharmaceutically effective amount of a pharmaceutical composition comprising a compound according to any one of the formulae I through II shown above, wherein R^1 through R^{15}, n, Y and Z all have the same definitions as those given above.

Any of the compounds of the present invention can be synthesized as pharmaceutically acceptable salts for incorporation into various pharmaceutical compositions. As used herein, pharmaceutically acceptable salts include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, hydrofluoric, sulfuric, citric, maleic, acetic, lactic, nicotinic, succinic, oxalic, phosphoric, malonic, salicylic, phenylacetic, stearic, pyridine, ammonium, piperazine, diethylamine, nicotinamide, formic, urea, sodium, potassium, calcium, magnesium, zinc, lithium, cinnamic, methylamino, methanesulfonic, picric, tartaric, triethylamino, dimethylamino, and tris(hydroxymethyl)aminomethane. Additional pharmaceutically acceptable salts are known to those skilled in the art.

PR modulator compounds of the present invention may be particularly useful for female hormone replacement therapy and as modulators of fertility (*e.g.*, as contraceptives, contragestational agents or abortifacients, *in vitro* fertilization, pregnancy maintenance), either alone or in conjunction with one or more estrogen receptor

modulators. PR modulator compounds of this invention also may be used in the treatment of dysfunctional uterine bleeding, dysmenorrhea, endometriosis, leiomyomas (uterine fibroids), hot flushes, mood disorders, and meningiomas. PR modulator compounds of this invention also may be used in the treatment of various hormone-dependent cancers, including, without limitation, cancers of ovaries, breast, endometrium and prostate. PR modulator compounds of this invention can also be used in treatment of female osteoporosis, either alone or in combination with one or more estrogen receptor modulators.

It will be understood by those skilled in the art that while the compounds of the present invention will typically be employed as a selective agonists, partial agonists or antagonists, there may be instances where a compound with a mixed steroid receptor profile is preferred. For example, use of a PR agonist (*i.e.*, progestin) in female contraception often leads to the undesired effects of increased water retention and acne flare ups. In this instance, a compound that is primarily a PR agonist, but also displays some AR and MR modulating activity, may prove useful. Specifically, the mixed MR effects would be useful to control water balance in the body, while the AR effects would help to control any acne flare ups that occur.

Furthermore, it will be understood by those skilled in the art that the compounds of the present invention, typically pharmaceutical compositions and formulations containing one or more of these compounds, can be used in a wide variety of combination therapies to treat the conditions and diseases described above. Thus, the compounds of the present invention can be used in combination with other hormones and other therapies, including, without limitation, chemotherapeutic agents such as cytostatic

and cytotoxic agents, immunological modifiers such as interferons, interleukins, growth hormones and other cytokines, hormone therapies, surgery and radiation therapy.

Representative PR modulator compounds (*i.e.*, agonists, partial agonists and antagonists) according to the present invention include:

9-Fluoro-5-(1,3-dithia-2-cyclohexylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **10**);

8-methoxy-5-(1,3-dithia-2-cyclohexylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **13**);

7,9-difluoro-5-(1,3-dithia-2-cyclohexylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **15**);

7-fluoro-5-(1,3-dithia-2-cyclohexylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **17**);

7-fluoro-5-cyclohexylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **19**);

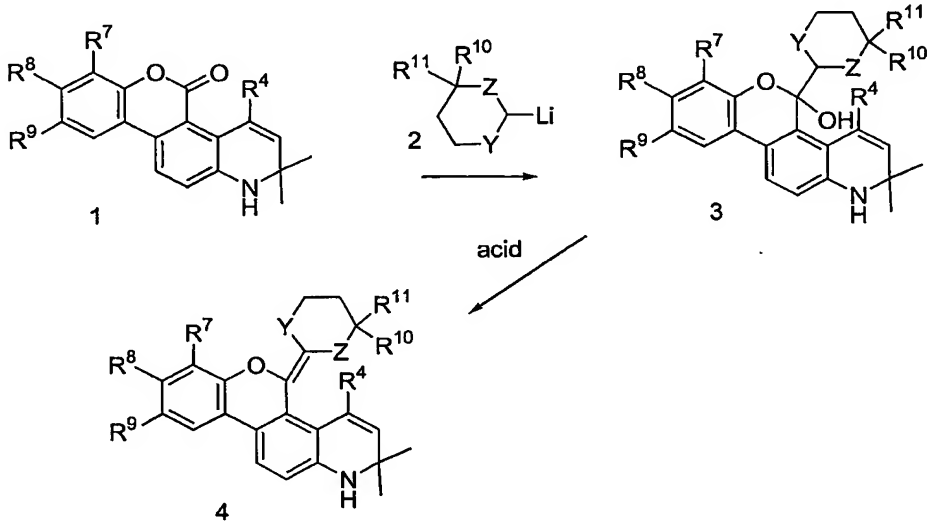
7,9-difluoro-5-cyclohexylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **20**);

7-fluoro-5-(1,3-dithia-2-cyclohexylidene)-1,2-dihydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **21**); and

7-fluoro-5-(2-cyclohexenylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **23**).

The sequence of steps for the general schemes to synthesize the compounds of the present invention is shown below. In each of the Schemes the R groups (*e.g.*, R^1, R^2, *etc.*) correspond to the specific substitution patterns noted in the Examples. However, it will be understood by those skilled in the art that other functionalities disclosed herein at the indicated positions of compounds of formulae I and II also comprise potential substituents for the analogous positions on the structures within the Schemes. In a further aspect, the present invention contains a novel process for the preparation of the compounds of the present invention.

Scheme I



The process of Scheme I begins with addition of lithium reagents **2** to lactones **1** that were previously disclosed (Todd, Jones; *et al.* US Patent Nos. 5,693,646; 5,693,647 and 5,696,127) to produce hemiacetal **3**. Treatment of the intermediate **3** with a Lewis acid, such as p-toluenesulfonic acid, affords the cyclic alkylidenes **4**.

The compounds of the present invention also include racemates, stereoisomers and mixtures of said compounds, including isotopically-labeled and radio-labeled

compounds. Such isomers can be isolated by standard resolution techniques, including fractional crystallization and chiral column chromatography.

As noted above, any of the PR modulator compounds of the present invention can be combined in a mixture with a pharmaceutically acceptable carrier to provide pharmaceutical compositions useful for treating the biological conditions or disorders noted herein in mammalian, and particularly in human patients. The particular carrier employed in these pharmaceutical compositions may take a wide variety of forms depending upon the type of administration desired. Suitable administration routes include enteral (*e.g.*, oral), topical, suppository, inhalable and parenteral (*e.g.*, intravenous, intramuscular and subcutaneous).

In preparing the compositions in oral liquid dosage forms (*e.g.*, suspensions, elixirs and solutions), typical pharmaceutical media, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be employed. Similarly, when preparing oral solid dosage forms (*e.g.*, powders, tablets and capsules), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like will be employed. Due to their ease of administration, tablets and capsules represent a desirable oral dosage form for the pharmaceutical compositions of the present invention.

For parenteral administration, the carrier will typically comprise sterile water, although other ingredients that aid in solubility or serve as preservatives may also be included. Furthermore, injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like will be employed.

For topical administration, the compounds of the present invention may be formulated using bland, moisturizing bases, such as ointments or creams. Examples of suitable ointment bases are petrolatum, petrolatum plus volatile silicones, lanolin and water in oil emulsions such as Eucerin™, available from Beiersdorf (Cincinnati, Ohio). Examples of suitable cream bases are Nivea™ Cream, available from Beiersdorf (Cincinnati, Ohio), cold cream (USP), Purpose Cream™, available from Johnson & Johnson (New Brunswick, New Jersey), hydrophilic ointment (USP) and Lubriderm™, available from Warner-Lambert (Morris Plains, New Jersey).

The pharmaceutical compositions and compounds of the present invention will generally be administered in the form of a dosage unit (*e.g.*, tablet, capsule, etc.). The compounds of the present invention generally are administered in a daily dosage of from about 1 μg/kg of body weight to about 50 mg/kg of body weight. Typically, the compounds of the present invention are administered in a daily dosage of from about 2 μg/kg to about 25 mg/kg of body weight. Most often, the compounds of the present invention are administered in a daily dosage of from about 10 μg/kg to about 5 mg/kg body weight. As recognized by those skilled in the art, the particular quantity of pharmaceutical composition according to the present invention administered to a patient will depend upon a number of factors, including, without limitation, the biological activity desired, the condition of the patient, and tolerance for the drug.

Compounds of this invention also have utility when radio- or isotopically-labeled as ligands for use in assays to determine the presence of PR in a cell background or extract. They may be particularly useful due to their ability to selectively activate progesterone receptors, and can therefore be used to determine the presence of such receptors in the presence of other steroid receptors or related intracellular receptors.

The compounds and pharmaceutical compositions of the present invention may be extremely potent activators of PR. For example, the compounds and compositions of the present invention may display 50% maximal activation of PR at a concentration of less than 50 nM. Some compounds and compositions of the present invention may display 50% maximal activation of PR at a concentration of less than 20 nM, and some may display such activity at a concentration of less than 10 nM.

The invention will be further illustrated by reference to the following non-limiting Examples.

EXAMPLE 1

Preparation of 9-Fluoro-5-(1,3-dithia-2-cyclohexylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **10**, Structure **4** of Scheme I, where R^4 = methyl, $R^7 = R^8 = R^{10} = R^{11}$ = H, R^9 = F, Y = Z = S).

To a solution of 1,3-dithiane (0.24 g, 2.0 mmol) in THF (10 mL) at –70°C was added *n*-BuLi (1.6 M in hexane, 1.3 mL) and the resulting mixture was stirred at –10°C for 2 h. To the reaction mixture at –70°C was added 9-fluoro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound **11**, Structure **1** of Scheme I, where R^4 = methyl, $R^7 = R^8$ = H, R^9 = F) (0.12 g, 0.40 mmol) in THF (1 mL). The dark red solution was slowly warmed to –30°C till the red color faded away and was quenched immediately with water. Extraction with EtOAc and chromatography afforded 9-fluoro-5-(1,3-dithia-2-cyclohexyl)-5-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **12**, Structure **3** of Scheme I, where R^4 = methyl, $R^7 = R^8 = R^{10} = R^{11}$ = H, R^9 = F, Y = Z = S), which was then treated in CH_2Cl_2 (10 mL) with catalytic amount of TsOH for 15 h. The reaction was quenched with aqueous carbonate and extracted with EtOAc. Chromatography provided compound **10** (70 mg, 42%) as a

yellow solid: mp 120-122°C, ^{1}H-NMR (400 MHz, $CDCl_3$) 7.34 (d, J = 8.3, 1H), 7.32 (dd, J = 9.7 and 2.9, 1H), 7.07 (dd, J = 8.7 and 4.9, 1H), 6.84 (td, J = 8.4 and 2.8, 1H), 6.62 (d, J = 8.3, 1H), 5.48 (s, 1H), 4.17 (s, 1H), 3.02 (ddd, J = 13.4, 8.2 and 5.1, 1H), 2.91-2.79 (m, 2H), 2.68 (dt, J = 13.4 and 5.5, 1H), 2.20-2.04 (m, 2H), 1.99 (s, 3H), 1.41 (s, 3H) and 1.28 (s, 3H).

EXAMPLE 2

Preparation of 8-methoxy-5-(1,3-dithia-2-cyclohexylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **13**, Structure **4** of Scheme I, where R^4 = methyl, $R^7 = R^9 = R^{10} = R^{11}$ = H, R^8 = methoxy, Y = Z = S).

This compound was prepared in a similar fashion as that described in Example **1** from 1,3-dithiane and 8-methoxy-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound **14**, Structure **1** of Scheme I, where R^4 = methyl, $R^7 = R^9$ = H, R^8 = methoxy) as a yellow solid: ^{1}H-NMR (400 MHz, $CDCl_3$) 7.39 (d, J = 8.2, 1H), 7.20 (d, J = 2.9, 1H), 7.07 (d, J = 8.9, 1H), 6.73 (dd, J = 8.9, 2.9, 1H), 6.63 (d, J = 8.2, 1H), 5.47 (s, 1H), 4.1 (bs, 1H), 3.82 (s, 3H), 3.04-2.98 (m, 1H), 2.89-2.78 (m, 2H), 2.68-2.64 (m, 1H), 2.16-2.03 (m, 2H), 1.99 (s, 3H), 1.41 (s, 3H), 1.25 (s, 3H) .

EXAMPLE 3

Preparation of 7,9-difluoro-5-(1,3-dithia-2-cyclohexylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **15**, Structure **4** of Scheme I, where R^4 = methyl, $R^8 = R^{10} = R^{11}$ = H, $R^7 = R^9$ = fluorine, Y = Z = S).

This compound was prepared in a similar fashion as that described in Example **1** from 1;3-dithiane and 7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound **16**, Structure **1** of Scheme I, where R^4 = methyl, $R^7 = R^9$ =

fluorine, R^8 = H) as a yellow solid: ^{1}H-NMR (500 MHz, $CDCl_3$) 7.31 (d, J = 8.2, 1H), 7.14-7.11 (m, 1H), 6.72 (ddd, J = 10.1, 8.2, 2.7, 1H), 6.62 (d, J = 8.2, 1H), 5.48 (s, 1 H), 4.18 (bs, 1H), 3.07-3.01 (m, 1H), 2.92-2.82 (m, 2H), 2.72-2.67 (m, 1H), 2.18-2.07 (m, 2H), 1.99 (d, J = 1.2, 3H), 1.41 (s, 3H), 1.28 (s, 3H).

EXAMPLE 4

Preparation of 7-fluoro-5-(1,3-dithia-2-cyclohexylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **17**, Structure **4** of Scheme I, where R^4 = methyl, $R^8 = R^9 = R^{10} = R^{11}$ = H, R^7 = fluorine, Y = Z = S).

This compound was prepared in a similar fashion as that described in Example **1** from 1,3-dithiane and 7-fluoro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound **18**, Structure **1** of Scheme I, where R^4 = methyl, R^7 = fluorine, $R^8 = R^9$ = H) as a yellow solid: ^{1}H-NMR (500 MHz, $CDCl_3$) 7.44-7.42 (m, 1H), 7.42 (d, J = 8.2, 1H), 6.98-6.94 (m, 2H), 6.64 (d, J = 8.2, 1H), 5.49 (d, J = 1.5, 1H), 4.14 (bs, 1H), 3.08-3.02 (m, 1H), 2.93-2.82 (m, 2H), 2.72-2.66 (m, 1H), 2.18-2.06 (m, 2H), 2.01 (d, J = 1.2, 3H), 1.42 (s, 3H), 1.29 (s, 3H).

EXAMPLE 5

Preparation of 7-fluoro-5-cyclohexylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **19**, Structure **4** of Scheme I, where R^4 = methyl, $R^8 = R^9 = R^{10} = R^{11}$ = H, R^7 = fluorine, Y = Z = CH_2).

This compound was prepared in a similar fashion as that described in Example **1** from cyclohexylithium and 7-fluoro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound **18**, Structure **1** of Scheme I, where R^4 = methyl, R^7 = fluorine, $R^8 = R^9$ = H) as a yellow solid: ^{1}H-NMR (500 MHz, $CDCl_3$) 7.43-7.40 (m, 1H), 7.41 (d,

J=8.2, 1 H), 6.96-6.86 (m, 2H), 6.61 (d, J = 8.2, 1H), 5.45 (s, 1 H), 4.07 (bs, 1H), 3.03 (ddd, J = 14.0, 4.9, 4.9, 1H), 2.21-2.08 (m, 2H), 1.99 (d, J = 1.2, 3H), 1.92-1.86 (m, 1H), 1.76-1.70 (m, 1H), 1.62-1.57 (m, 2H), 1.45-1.24 (m, 3H), 1.40 (s, 3H), 1.18 (s, 3H) .

EXAMPLE 6

Preparation of 7,9-difluoro-5-cyclohexylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **20**, Structure **4** of Scheme I, where $R^8 = R^{10} = R^{11} = H$, R^4 = methyl, $R^7 = R^9$ = fluorine, Y = Z = CH_2).

This compound was prepared in a similar fashion as that described in Example **1** from cyclohexylithium and 7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound **16**, Structure **1** of Scheme I, where R^4 = methyl, $R^7 = R^9$ = fluorine, R^8 = H) as a yellow solid: ^{1}H-NMR (500 MHz, $CDCl_3$) 7.32 (d, J = 8.2, 1H), 7.14-7.11 (m, 1H), 6.70 (ddd, J = 10.4, 8.5, 2.8, 1H), 6.61 (d, J = 8.2, 1H), 5.45 (s, 1H), 4.12 (bs, 1H), 3.05-3.01 (m, 2H), 2.20-2.08 (m, 2H), 1.97 (d, J = 1.2, 3H), 1.91-1.85 (m, 1H), 1.78-1.71 (m, 1H), 1.63-1.58 (m, 2H), 1.45-1.23 (m, 3H), 1.40 (s, 3H), 1.18 (s, 3H).

EXAMPLE 7

Preparation of 7-fluoro-5-(1,3-dithia-2-cyclohexylidene)-1,2-dihydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **21**, Structure **4** of Scheme I, where $R^4 = R^8 = R^9 = R^{10} = R^{11} = H$, R^7 = fluorine, Y = Z = S).

This compound was prepared in a similar fashion as that described in Example **1** from 1,3-dithiane and 7-fluoro-1,2-dihydro-2,2-dimethyl-5-coumarino[3,4-*f*]quinoline (Compound **22**, Structure **1** of Scheme I, where R^7 = fluorine, $R^4 = R^8 = R^9$ = H) as a yellow solid: ^{1}H-NMR (500 MHz, $CDCl_3$) 7.39-7.36 (m, 1H), 7.36 (d, J = 8.2, 1H), 6.96-6.93 (m, 2H), 6.55 (d, J = 8.8, 1H), 6.31 (d, J = 10.1, 1H), 5.59 (d, J = 9.8, 1H), 4.0 (bs,

1H), 3.14-3.07 (m, 1H), 2.96-2.84 (m, 2H), 2.80-2.74 (m, 1H), 2.22-2.08 (m, 2H), 1.42 (s, 3H), 1.32 (s, 3H).

EXAMPLE 8

Preparation of 7-fluoro-5-(2-cyclohexenylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **23**, Structure **4** of Scheme I, where R^4 = methyl, $R^8 = R^9 = R^{11}$ = H, R^7 = fluorine, R^{10}/R^{14} = a bond, Z = CHR^{14}, Y = CH_2).

This compound was prepared in a similar fashion as that described in Example **1** from cyclohexenylithium and lactone **18** (Structure **1** of Scheme I, where R^4 = methyl, R^7 = fluorine, $R^8 = R^9$ = H) as a yellow solid: ^{1}H-NMR (500 MHz, Acetone-d_6) 7.57-7.54 (m, 1H), 7.54 (d, *J* = 8.2, 1H), 7.04-6.97 (m, 2H), 6.77 (d, *J* = 8.2, 1H), 6.11 (ddd, *J* = 10.1, 2.1, 1.8, 1H), 5.84-5.79 (m, 2H), 5.45 (s, 1H), 2.96-2.88 (m, 2H), 2.61-2.55 (m, 1H), 2.20-2.13 (m, 1H), 1.93 (d, *J* =1.2, 3H), 1.81-1.70 (m, 2H), 1.40 (s, 3H), 1.21 (s, 3H).

The activity of selected steroid receptor modulator compounds of the present invention were evaluated utilizing the cotransfection assay, and in standard receptor competitive binding assays, according to the following illustrative Examples.

EXAMPLE 9

Cotransfection assay

The function and detailed preparation procedure of the cotransfection assays have been described previously (Pathirana, C. *et al.*, Nonsteroidal Human Progesterone Receptor Modulators from the Marine Alga Cymopolia Barbata. *Mol. Pharm.* **1995**, *47*, 630-635). Briefly, the cotransfection assays were carried out in CV-1 cells (African green monkey kidney fibroblasts), which were transiently transfected, by the standard

calcium phosphate coprecipitation procedure (Berger, T. S. *et al.*, Interaction of Glucocorticoid Analogues with the Human Glucocorticoid Receptor. *J. Steroid Biochem. Mol. Bio.* **1992**, *41*, 733-738) with the Plasmid containing receptor, MTV-LUC reporter, pRS-β-Gal, and filler DNA (Rous sarcoma virus chloramphenicol acetyltransferase). The agonist activity was determined by examining the LUC expression (normalized response) and the efficacy readout was a relative value to the maximal LUC expression produced by progesterone. All the cotransfection experiments were carried out in 96-well plates by automation (Beckman Biomomek automated workstation).

Receptor Binding Assays

The preparation of receptor binding assays for hPR-A was described in literature (Pathirana, C. *et al.*, Nonsteroidal Human Progesterone Receptor Modulators from the Marine Alga Cymopolia Barbata. *Mol. Pharm.* **1995**, *47*, 630-635.)

The agonist, antagonist and binding activity assay results of selected progesterone receptor modulator compounds of the present invention and the standard reference compounds on PR are shown in Table 1 below. Efficacy is reported as the percent maximal response observed for each compound relative to the reference agonist and antagonist compounds indicated above. Also reported in Table 1 for each compound is its antagonist potency or IC_{50} (which is the concentration (nM), required to reduce the maximal response by 50%), and its agonist potency or EC_{50} (nM), which is the effective concentration that produced 50% of the maximum response.

Table 1: Agonist, antagonist and binding activity of progesterone receptor modulator compounds of present invention and the reference agonist compound, progesterone (Prog), and reference antagonists compound, RU486 and ZK299.

Cmpd	PR Agonist CV-1 Cells		PR Antagonist CV-1 Cells		PR Binding
No.	Efficacy (%)	Potency (nM)	Efficacy (%)	Potency (nM)	K_i (nM)
Prog	100	2.9	na	na	3.5
RU486	na	na	96	0.18	0.58
ZK299	na	na	99	1.6	18
10	144	2.0	na	na	6.3
13	56	32	na	na	14
15	155	5.3	na	na	3.7
17	107	11	na	na	4.3
19	48	38	nt	nt	74
20	82	16	na	na	39
21	45	32	nt	nt	nt
23	70	35	na	na	22

na = not active (*i.e.* efficacy of <20 and potency of >1,000)
nt = not tested

Pharmacological and Other Applications

The following Example provides illustrative pharmaceutical composition formulations:

EXAMPLE 10

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
COMPOUND **10**	10
Starch, dried	100
Magnesium stearate	10
Total	120 mg

The above ingredients are mixed and filled into hard gelatin capsules in 120 mg quantities.

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
COMPOUND **10**	10
Cellulose, microcrystalline	200
Silicon dioxide, fumed	10
Stearic acid	10
Total	230 mg

The components are blended and compressed to form tablets each weighing 230 mg.

Tablets, each containing 10 mg of active ingredient, are made as follows:

	Quantity (mg/tablet)
COMPOUND **10**	10
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (PVP) (as 10% solution in water)	4
Sodium carboxymethyl starch (SCMS)	4.5
Magnesium stearate	0.5
Talc	1.0
Total	100 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of PVP is mixed with the resultant powders, which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The SCMS, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Suppositories, each containing 225 mg of active ingredient, may be made as follows:

	Quantity (mg/suppository)
COMPOUND **10**	20
Saturated fatty acid glycerides	2,000
Total	2,020 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of normal 2 g capacity and allowed to cool.

An intravenous formulation may be prepared as follows:

	Quantity
COMPOUND **10**	10 mg
isotonic saline	1000 mL
glycerol	100 mL

The compound is dissolved in the glycerol and then the solution is slowly diluted with isotonic saline. The solution of the above ingredients is then administered intravenously at a rate of 1 mL per minute to a patient.

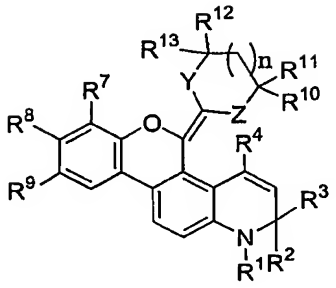
The present invention includes any combination of the various species and subgeneric groupings falling within the generic disclosure. This invention therefore includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

The scope of the invention is not to be limited by the description of the examles. Modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific examples which have been presented by way of example.

What is claimed is:

1. A compound of the formula:



(I)

wherein:

R^1 is selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 haloalkyl, C_1–C_4 heteroalkyl, COR^5, CO_2R^5, SO_2R^5, and $CONR^5R^6$;

R^2 and R^3 each independently is selected from the group of hydrogen, C_1–C_6 alkyl, and C_1–C_6 haloalkyl; or

R^2 and R^3 taken together form a cycloalkyl ring of from three to twelve carbons;

R^4 is selected from the group of hydrogen, F, Cl, Br, CN, OR^5, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl;

R^5 and R^6 each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^7 through R^9 each independently is selected from the group of hydrogen, F, Cl, Br, I, NO_2, CN, OR^5, NR^5R^6, SR^5, COR^5, CO_2R^5, $CONR^5R^6$, C_1–C_8 alkyl, C_1–C_8 heteroalkyl, C_1–C_8 haloalkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl;

R^{10} through R^{15} each independently is selected from the group of hydrogen, F, Cl, Br, OR^5, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl; or

R^{12} and R^{14} taken together form a bond, when Y is $CR^{14}R^{15}$; or

R^{10} and R^{14} taken together form a bond, when Z is $CR^{14}R^{15}$;

Y and Z each independently is selected from the group of O, S, NR^6 and $CR^{14}R^{15}$;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt or prodrug thereof.

2. A compound according to claim 1, wherein

R^1 is selected from the group of hydrogen, C_1–C_4 alkyl, COR^5, CO_2R^5, and SO_2R^5;

R^2 and R^3 each independently is selected from the group of C_1–C_4 alkyl;

R^4 is selected from the group of hydrogen, F, Cl, Br, C_1–C_4 alkyl, and C_1–C_4 haloalkyl;

R^5 and R^6 each is independently selected from the group of hydrogen, and C_1–C_4 alkyl;

R^7 through R^9 each independently is selected from the group of hydrogen, F, Cl, Br, CN, OR^5, C_1–C_8 alkyl, C_1–C_8 heteroalkyl, and C_1–C_8 haloalkyl;

R^{10} through R^{15} each independently is selected from the group of hydrogen, F, Cl, OR^5, C_1–C_4 alkyl, C_1–C_4 haloalkyl; or

R^{12} and R^{14} taken together form a bond, when Y is $CR^{14}R^{15}$; or

R^{10} and R^{14} taken together form a bond, when Z is $CR^{14}R^{15}$;

Y and Z each independently is selected from the group of S, and $CR^{14}R^{15}$; and n is 0, 1, or 2.

3. A compound according to claim 2, wherein

R^1 is hydrogen;

R^2 and R^3 is CH_3;

R^4 is selected from the group of F, Cl, Br, CH_3, and CF_3;

R^7 is hydrogen or F;

R^8 is selected from the group of H, CH_3, OH, and OCH_3;

R^9 is selected from the group of hydrogen, F, Cl, Br, CN, OCH_3, CH_3, and CF_3;

R^{10}, R^{11}, R^{13}, R^{15} each independently is selected from the group of hydrogen, F, Cl, CH_3, and CF_3; and

R^{12} and R^{14} taken together form a bond, when Y is $CR^{14}R^{15}$.

4. A compound according to claim 1, wherein said compound is selected from the group of:

9-Fluoro-5-(1,3-dithia-2-cyclohexylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **10**);

8-methoxy-5-(1,3-dithia-2-cyclohexylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **13**);

7,9-difluoro-5-(1,3-dithia-2-cyclohexylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **15**);

7-fluoro-5-(1,3-dithia-2-cyclohexylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **17**);

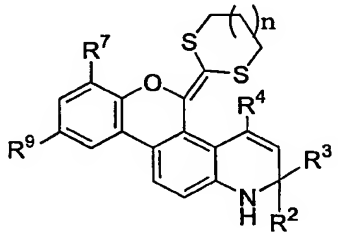
7-fluoro-5-cyclohexylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **19**);

7,9-difluoro-5-cyclohexylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **20**);

7-fluoro-5-(1,3-dithia-2-cyclohexylidene)-1,2-dihydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **21**); and

7-fluoro-5-(2-cyclohexenylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **23**).

5. A compound of the formula:



(II)

wherein:

R^2 and R^3 each independently is selected from the group of C_1–C_4 alkyl, and C_1–C_4 haloalkyl;

R^4 is selected from the group of hydrogen, F, Cl, Br, CN, OR^5, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl;

R^5 and R^6 each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^7 through R^9 each independently is selected from the group of hydrogen, F, Cl, Br, CN, OR^5, NR^5R^6, SR^5, COR^5, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, C_1–C_4 haloalkyl, C_2–C_4 alkenyl;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt or prodrug thereof.

6. A compound according to claim 5, wherein

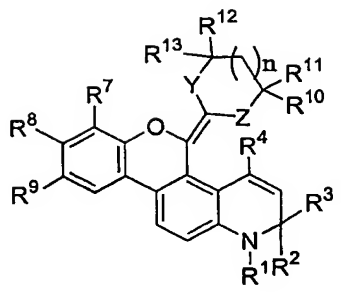
R^2 and R^3 is CH_3;

R^4 is selected from the group of F, Cl, Br, CH_3, and CF_3;

R^7 is hydrogen or F;

R^9 is selected from the group of hydrogen, F, Cl, Br, CN, OCH_3, CH_3, and CF_3.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula:



(I)

wherein:

R^1 is selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 haloalkyl, C_1–C_4 heteroalkyl, COR^5, CO_2R^5, SO_2R^5, and $CONR^5R^6$;

R^2 and R^3 each independently is selected from the group of hydrogen, C_1–C_6 alkyl, and C_1–C_6 haloalkyl; or

R^2 and R^3 taken together form a cycloalkyl ring of from three to twelve carbons;

R^4 is selected from the group of hydrogen, F, Cl, Br, CN, OR^5, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl;

R^5 and R^6 each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^7 through R^9 each independently is selected from the group of hydrogen, F, Cl, Br, I, NO_2, CN, OR^5, NR^5R^6, SR^5, COR^5, CO_2R^5, $CONR^5R^6$, C_1–C_8 alkyl, C_1–C_8 heteroalkyl, C_1–C_8 haloalkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl;

R^{10} through R^{15} each independently is selected from the group of hydrogen, F, Cl, Br, OR^5, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl; or

R^{12} and R^{14} taken together form a bond, when Y is $CR^{14}R^{15}$; or

R^{10} and R^{14} taken together form a bond, when Z is $CR^{14}R^{15}$;

Y and Z each independently is selected from the group of O, S, NR^6 and $CR^{14}R^{15}$;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt or prodrug thereof.

8. A pharmaceutical composition according to claim 7, wherein:

R^1 is selected from the group of hydrogen, C_1–C_4 alkyl, COR^5, CO_2R^5, and SO_2R^5;

R^2 and R^3 each independently is selected from the group of C_1–C_4 alkyl;

R^4 is selected from the group of hydrogen, F, Cl, Br, C_1–C_4 alkyl, and C_1–C_4 haloalkyl;

R^5 and R^6 each is independently selected from the group of hydrogen, and C_1–C_4 alkyl;

R^7 through R^9 each independently is selected from the group of hydrogen, F, Cl, Br, CN, OR^5, C_1–C_8 alkyl, C_1–C_8 heteroalkyl, and C_1–C_8 haloalkyl;

R^{10} through R^{15} each independently is selected from the group of hydrogen, F, Cl, OR^5, C_1–C_4 alkyl, C_1–C_4 haloalkyl; or

R^{12} and R^{14} taken together form a bond, when Y is $CR^{14}R^{15}$; or

R^{10} and R^{14} taken together form a bond, when Z is $CR^{14}R^{15}$;

Y and Z each independently is selected from the group of S, and $CR^{14}R^{15}$;

n is 0, 1, or 2.

9. A pharmaceutical composition according to claim 8, wherein:

R^1 is hydrogen;

R^2 and R^3 is CH_3;

R^4 is selected from the group of F, Cl, Br, CH_3, and CF_3;

R^7 is hydrogen or F;

R^8 is selected from the group of H, CH_3, OH, and OCH_3;

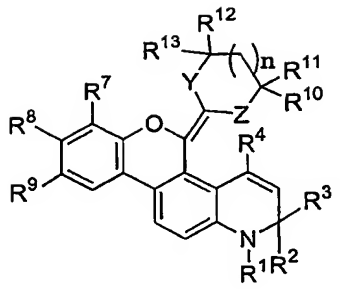
R^9 is selected from the group of hydrogen, F, Cl, Br, CN, OCH_3, CH_3, and CF_3;

R^{10}, R^{11}, R^{13}, R^{15} each independently is selected from the group of hydrogen, F, Cl, CH_3, and CF_3; and

R^{12} and R^{14} taken together form a bond, when Y is $CR^{14}R^{15}$.

10. A method of treating an individual having a condition mediated by a progesterone receptor comprising administering to said individual a pharmaceutically effective amount of a compound according to any one of claims 1, 4 and 5.

11. A method of treating an individual having a condition mediated by a progesterone receptor comprising administering to said individual a pharmaceutically effective amount of a compound represented by formula (I):



(I)

wherein:

R^1 is selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 haloalkyl, C_1–C_4 heteroalkyl, COR^5, CO_2R^5, SO_2R^5, and $CONR^5R^6$;

R^2 and R^3 each independently is selected from the group of hydrogen, C_1–C_6 alkyl, and C_1–C_6 haloalkyl; or

R^2 and R^3 taken together form a cycloalkyl ring of from three to twelve carbons;

R^4 is selected from the group of hydrogen, F, Cl, Br, CN, OR^5, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl;

R^5 and R^6 each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^7 through R^9 each independently is selected from the group of hydrogen, F, Cl, Br, I, NO_2, CN, OR^5, NR^5R^6, SR^5, COR^5, CO_2R^5, $CONR^5R^6$, C_1–C_8 alkyl, C_1–C_8 heteroalkyl, C_1–C_8 haloalkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl;

R^{10} through R^{15} each independently is selected from the group of hydrogen, F, Cl, Br, OR^5, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl; or

R^{12} and R^{14} taken together form a bond, when Y is $CR^{14}R^{15}$; or

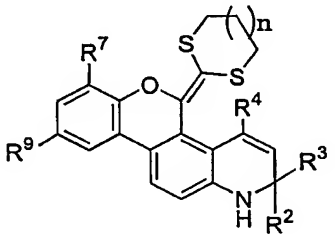
R^{10} and R^{14} taken together form a bond, when Z is $CR^{14}R^{15}$;

Y and Z each independently is selected from the group of O, S, NR^6 and $CR^{14}R^{15}$;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt or prodrug thereof.

12. A method of treating an individual having a condition mediated by a progesterone receptor comprising administering to said individual a pharmaceutically effective amount of a compound represented by formula (II):



(II)

wherein:

R^2 and R^3 each independently is selected from the group of C_1–C_4 alkyl, and C_1–C_4 haloalkyl;

R^4 is selected from the group of hydrogen, F, Cl, Br, CN, OR^5, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl;

R^5 and R^6 each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^7 through R^9 each independently is selected from the group of hydrogen, F, Cl, Br, CN, OR^5, NR^5R^6, SR^5, COR^5, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, C_1–C_4 haloalkyl, C_2–C_4 alkenyl;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt or prodrug thereof.

13. A method according to claim 10, wherein said condition is selected from the group of dysfunctional uterine bleeding, dysmenorrhea, endometriosis, leiomyomas (uterine fibroids), hot flushes, mood disorders, meningiomas, hormone-dependent cancers and female osteoporosis.

14. A method according to claim 10, wherein said condition is alleviated with female hormone replacement therapy.

15. A method of modulating the fertility of an individual comprising administering to said individual a pharmaceutically effective amount of a compound according to any one of claims 1, 4, and 5.

16. A method of modulating a progesterone receptor in an individual comprising administering to said individual a compound according to any one of claims 1, 4, and 5 in an amount effective to modulate a progesterone receptor.

17. A method according to claim 16, wherein said modulation is activation.

18. A method according to claim 17, wherein said compound provides at least 50% maximal activation of progesterone receptor at a drug concentration of less than 100 nM.

19. A method according to claim 17, wherein said compound provides at least 50% maximal activation of progesterone receptor at a drug concentration of less than 50 nM.

20. A method according to claim 17, wherein said compound provides at least 50% maximal activation of progesterone receptor at a drug concentration of less than 20 nM.

21. A method according to claim 17, wherein said compound provides at least 50% maximal activation of progesterone receptor at a drug concentration of less than 10 nM.

22. A method of treating an individual having cancer comprising administering to said individual a pharmaceutically effective amount of a compound according to any one of claims 1, 4 and 5.

23. A method according to claim 22, wherein said cancer is ovarian cancer, breast cancer, endometrial cancer or prostate cancer.

24. A method of determining the presence of a progesterone receptor (PR) in a cell or cell extract comprising (a) labeling a compound according to any one of claims 1, 4 or 5; (b) contacting the cell or cell extract with said labeled compound; and (c) testing the contracted cell or cell extract to determine the presence of progesterone receptor.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/24416

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D491/04 A61K31/44 A61P35/00 A61P19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ZHI, L. ET AL.: "Synthesis and Biological Activity of 5-Methylidene 1,2-Dihydrochromeno'3,4-f!quinoline Derivatives as Progesterone Receptor Modulators" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, 2003, pages 2071-2074, XP002267155 example 18; table 1 --- -/--	1-24

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 January 2004	18/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Baston, E

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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